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## **Prevention and Management of Ovarian Hyperstimulation Syndrome**

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## **Abstract**

Ovarian hyperstimulation syndrome (OHSS) is a serious iatrogenic complication of ovarian stimulation. It is feasible to identify patients at risk, modify stimulation strategies to ameliorate risk, and initiate out-patient treatments that alter disease pathophysiology to reduce disease severity. Mitigation of OHSS risk and severity, through innovative approaches prior to treatment, during treatment and after treatment should now be the standard care. This review summarizes recent developments and provides recommendations on the prevention and treatment of OHSS.

## Introduction

In vitro fertilisation (IVF) continues to transform lives around the world, with refinements in clinical and laboratory techniques driving an incessant improvement in outcomes. In particular, the adoption of pre-treatment biomarkers to individualise doses of exogenous gonadotrophins, use of gonadotrophin releasing hormone (GnRH) antagonists for prevention of premature luteinising hormone (LH) surges, the shift from using human chorionic gonadotrophin (hCG) to trigger final oocyte maturation prior to oocyte retrieval to use of GnRH agonists to induce an endogenous LH surge, and segmentation of the cycle by temporally separating the stimulation and embryo transfer by freezing all embryos, all have the potential to dramatically enhance the efficacy and safety of IVF.

Unfortunately failure to comprehensively adopt these strategies, means that ovarian hyperstimulation syndrome (OHSS) is a potentially lethal iatrogenic complication of the early luteal phase and/or early pregnancy after ovarian stimulation [1-3]. OHSS has historically been classified on severity (mild, moderate, severe, critical) (Table 1) and by timing early (<9days) or late. Focus has however shifted to moderate or severe OHSS which affects 2-3% of patients, as milder forms may develop in 20-30% of all in-vitro fertilisation (IVF) cycles, and it is the moderate/severe OHSS which incurs risk of acute renal insufficiency, acute respiratory distress syndrome and venous thromboembolism [4]. Given the multiple classification systems available and potential for ascertainment bias, an objective reproducible pathway for OHSS classification has now been proposed for use in clinical trial reporting (Figure 1, Table 2), which complements existing clinical guidelines [1-4].

The pathophysiological changes of OHSS that underlie these events include arteriolar vasodilatation and increased capillary permeability. This facilitates a shift in fluid from the intra- to the extra-vascular compartment and the induction of a state of hypovolaemic hyponatremia with haemoconcentration. Although various systemic and local vasoactive mediators contribute to the pathogenesis of OHSS, vascular endothelial growth factor (VEGF) appears to be critical to the development of the condition [5]. VEGF is involved in corpus follicular growth, luteum function, angiogenesis, and vascular endothelial stimulation. In response to human chorionic gonadotrophin (hCG), VEGF mediates the vascular permeability of OHSS the cardinal feature of the syndrome [5]. It is this induction by hCG

that ensures OHSS is primarily self-limiting in those who are not pregnant but also why it may persist into the first trimester due to ongoing stimulation of the ovaries. Recognition of the critical contribution of hCG and VEGF to the pathogenesis of OHSS has facilitated successful treatment modification incorporating gonadotrophin antagonist control, agonist triggering and novel dopamine agonist preventative measures [1, 2]. The current review aims to summarise the latest evidence on the identification of patients at risk of OHSS, preventative measures and the treatment of OHSS.

### **Who is at risk of moderate or severe OHSS?**

There are several pre-treatment characteristics such as young age, black race, ovulation disorder and polycystic ovarian syndrome (PCOS), which have been consistently associated with an increased risk of OHSS [6]. However, these are common risk factors and as such are not particularly useful in pre-treatment stratification of risk. In contrast biomarkers of the ovarian reserve and in particular an elevated anti-müllerian hormone (AMH)( $>3.4\text{ng/ml}$ ) or elevated antral follicle count (AFC)( $>24$ ), have been proven to be significantly more specific and sensitive and are now routinely recommended for the pre-treatment identification of patients at risk and for planning of ovarian stimulation cycles [1, 7]. Once patients have commenced treatment, additional characteristics related to the extent of multifollicular growth such as a visualisation of a  $\geq 25$  follicles, oestradiol on the day of trigger  $>3,500\text{ pg/ml}$  or  $\geq 24$  oocytes retrieved may aid in the prediction of patients who will develop OHSS [1].

### **How can we prevent OHSS?**

#### *Use gonadotrophin-releasing hormone antagonists*

There are multiple trials demonstrating a reduction in OHSS by use of gonadotrophin-releasing hormone (GnRH) antagonists for ovulation suppression as compared to GnRH agonist control [8]. The most recent Cochrane meta-analysis incorporating data from 20 RCTs and 5141 patients suggested that use of GnRH antagonists was associated with a reduction in moderate and severe OHSS (OR 0.53 (95% CI 0.40, 0.69)) despite similar pregnancy and live-birth rates [8]. Notably many of the trials included in the meta-analysis were done in high-risk patients. However, recent confirmation of the efficacy of GnRH antagonists for a reduction in OHSS was obtained by an RCT of 1050 unselected women having their first treatment cycle (OR 0.43, 95% CI 0.33, 0.57) [9]. That live-birth rates were

similar for both treatment arms would suggest that a GnRH antagonist protocol would be the treatment of choice for the first IVF cycle in women <40years old [9].

#### *Avoid aggressive ovarian stimulation*

Large scale population studies have demonstrated that cumulative live-birth rates plateau with oocyte yields  $\geq 15$ , but that the risk of OHSS increases substantively beyond this point [10]. Despite this, clinicians frequently use large doses of gonadotrophins to try to attain large oocyte yields in excess of 15 oocytes, with the underlying belief that this will improve the overall chances of success. However, large oocyte yields have not been shown to be accompanied by an increase in good-quality blastocysts [11], and RCTs have shown a decrease in fresh embryo transfer associated live-birth rates in women with high oocyte yields[12].

#### *Concomitant use of aspirin*

Aspirin inhibits platelet cyclooxygenase-1 (COX-1). A recent network meta-analysis suggested that aspirin (100mg/day) during ovarian stimulation, and continued until a negative pregnancy test or ultrasonographic evidence of embryonic cardiac activity may be a prophylactic regimen for OHSS (RR 0.07, 95% CI 0.07–0.30), with no detrimental side effects on clinical pregnancy rates [13]. It is noteworthy though that this beneficial effect was primarily driven by a large single centre study, with only two (0.25%) cases of severe or critical OHSS developing in the 780 high-risk patients treated with 100mg aspirin, as compared to 43 patients (8.4%) of the 412 who did not receive aspirin [14]. The only other smaller RCT (n=145) similarly reported a reduction in OHSS with aspirin [15]. To date there has not been widespread adoption of aspirin, with some, but not all recent guidelines supporting its use due to the limited evidence base [1, 2].

#### *Concomitant use of metformin*

Metformin an oral biguanide, is recognised to reduce OHSS in a GnRH-agonist IVF cycles (OR 0.29; 95% CI 0.18 to 0.49) [16]. However, its role in GnRH antagonist cycles is less clear, with the most recent trial not demonstrating an impact of metformin on the incidence of moderate–severe OHSS [17], as compared to the only other older and smaller trial reported [18]. Furthermore that treatment with metformin during ovarian stimulation was still associated with an overall occurrence of moderate–severe OHSS of 14.1% in cycles triggered

with hCG, is no longer acceptable given that a substantive reduction in OHSS may be achieved by simply replacing hCG with a GnRH agonist trigger.

#### *Avoid exogenous and endogenous hCG exposure*

The structural similarity of hCG to luteinising hormone (LH), contributed to its adoption as the standard “trigger” for induction of final oocyte maturation [19]. In the stimulated ovary the longer half-life of hCG ensures sustained stimulation of LH receptors on the multiple corpus lutea, but as the luteinising granulosa cells of the corpus lutea are a major source of VEGF this also incurs a risk of OHSS. Reduction in the doses of hCG used to trigger oocyte maturation have had inconsistent effects on OHSS rates. Alternative strategies such as replacement of the hCG trigger with a GnRH agonist trigger to induce an endogenous LH surge in GnRH antagonist controlled cycles and/or elective cryopreservation of all embryos and thereby limiting endogenous hCG exposure, have been examined.

Use of a GnRH agonist trigger alone is associated with a reduction in pregnancy rates in fresh transfers but not recipients of oocyte donors, suggesting that it compromises luteal function [20]. Although it is feasible to proceed to an embryo transfer after an agonist trigger by modifying the luteal support, this is still associated with a risk of OHSS irrespective of whether low dose hCG or purely exogenous steroid hormone support is provided [21, 22]. Consequently, the combination of an agonist trigger with elective cryopreservation of all embryos is now recognised as being highly effective at reducing the risk of OHSS [23]. Although initially touted as a means of achieving an OHSS free clinic [24], OHSS can still occur, albeit rarely. It should also be noted that patients who exhibit signs of significant suppression of the hypothalamic-pituitary axis, as determined by low serum LH ( $<0.5$  mIU/mL) on the day of trigger, have a 25% chance of a suboptimal response to use of a GnRH agonist for final oocyte maturation [25]. To overcome this inadequate response, dual triggering with hCG (1000IU) and GnRH agonist trigger have been used, but this negates the principal advantage of removing exogenous hCG, the principal driver of OHSS [26].

#### *Give a dopamine agonist after oocyte retrieval*

The dopamine-receptor agonist, cabergoline, partially inhibits the ovarian VEGF receptor 2 (VEGFR-2) through a decrease in its phosphorylation levels; such inhibition, in turn, decreases the VEGFR-2–induced vascular permeability, without affecting luteal angiogenesis [5]. Several trials have now demonstrated that cabergoline administration (0.5mg/day) from

the day of hCG administration in high risk women can reduce the incidence and severity of early OHSS in GnRH agonist IVF cycles, while not compromising pregnancy rates [27]. Alternative dopamine agonists; quinagolide and bromocriptine, have also been associated with a reduction in OHSS, but they have been less extensively studied.

#### *Consider calcium gluconate infusion after oocyte retrieval*

Low intracellular calcium has a stimulatory role on adenylyl cyclase resulting in cAMP synthesis and thus renin release. By increasing circulating calcium concentrations by infusion of calcium gluconate, it was speculated that this would inhibit cAMP-stimulated renin release, decrease angiotensin II synthesis and VEGF production. Several studies including one double-blind RCT of 200 women have supported this theory, with administration of 10mls of 10% calcium gluconate on the day of the oocyte retrieval and days 1, 2 and 3 after oocyte retrieval associated with a reduction on moderate and severe OHSS without compromising the pregnancy rate [13, 28].

#### *Perform single embryo-transfer*

If proceeding to a fresh embryo transfer, transfer of a single embryo will reduce the risk of late onset OHSS. Circulating hCG concentrations reflect the number of pregnancies and are higher in multiple pregnancies [6].

#### *Additional adjuvant therapies and alternative strategies*

A wide range of alternative strategies including administration of luteal antagonist, letrozole, methyprednisolone, ketocanazole administration have been reported as being associated with a reduction in OHSS but the data on these treatments is limited [1, 2]. Withholding FSH for up to 4 days (coasting), has not been associated with a reduced risk of OHSS in RCTs [1, 2]. Cancellation of the stimulation cycle and withholding hCG may prevent OHSS but strategies to prevent a spontaneous LH surge will be required.

### **How can we treat OHSS?**

Once OHSS develops, traditional management involved rest and observation until the clinical picture deteriorates sufficiently to require hospitalization. It is now recognised that the described preventative strategies may be coupled with a protocol for the active management of patients during the luteal phase, when they first manifest signs and symptoms of moderate



OHSS in an attempt to facilitate continued out-patient management [29]. For symptomatic women this entails critical fluid balance, with maintenance of oral fluid intake as guided by thirst to ensure intravascular perfusion and adequate diuresis, and commencement of prophylactic anticoagulation [1, 2]. Although there are no comparative studies addressing the value of thromboprophylaxis in women with severe OHSS, the use of prophylactic low molecular weight heparin (LMWH) prophylaxis is supported by the increased incidence of first trimester thrombosis in women with OHSS (16.8 VTE events per 1000 women, OR 99.7, 95% CI 61.6–161.1) as compared to non-IVF pregnancies (0.2 VTE events per 1000 women) [30]. Thrombosis in women with OHSS frequently affects upper body sites, and clinicians should remain vigilant of patients presenting with unusual symptoms such as dizziness, loss of vision and neck pain [31]. With respect to duration of prophylaxis, the increased VTE risk may extend beyond the first trimester, and consequently thromboprophylaxis should be considered at least until the end of the first trimester, with further treatment decided in conjunction with a specialist haematologist[3].

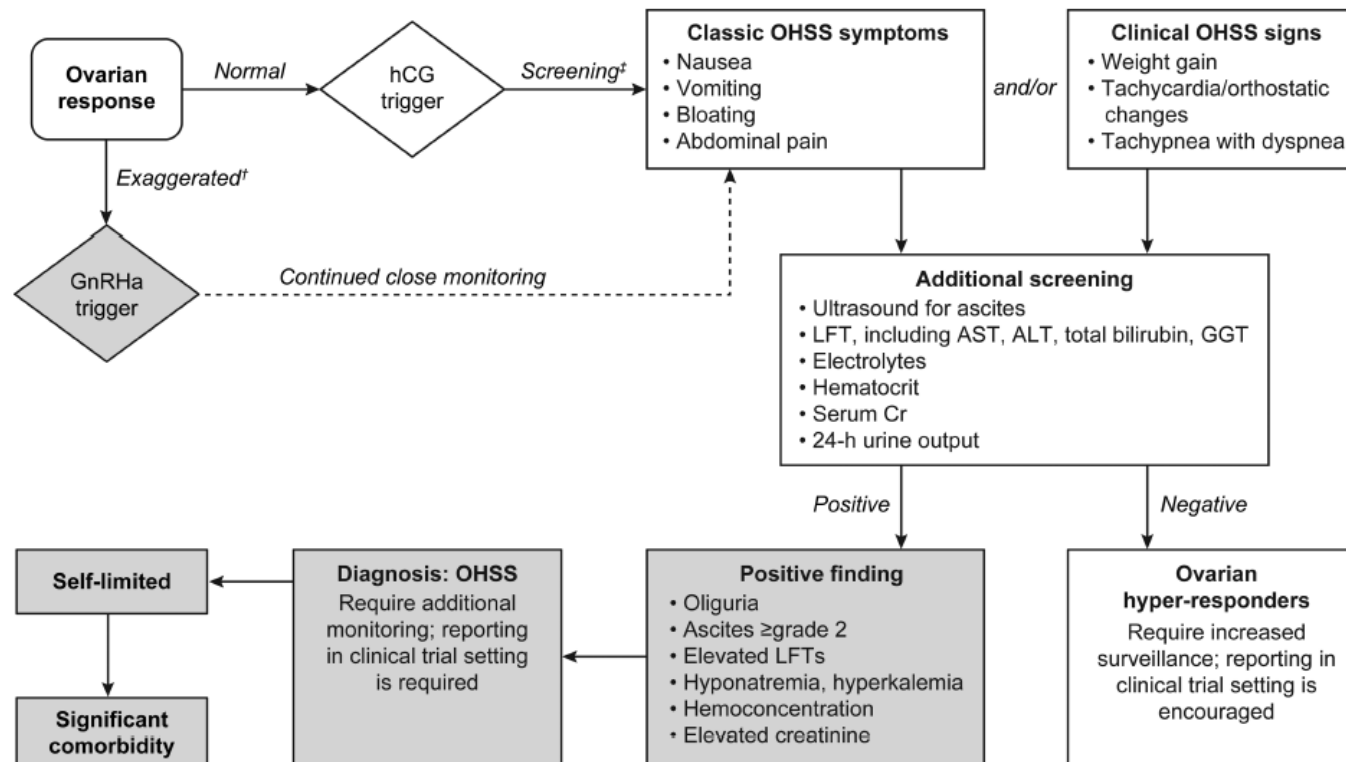
For those with ascites, ultrasounded guided paracentesis/culdocentesis, may be performed in an out-patient setting, in the same way that an oocyte retrieval is performed. Drainage of ascites with relief of abdominal distension, infusion of colloid, and correction of deficient oral intake may allow rapid correction of the hemoconcentration, electrolyte abnormalities and reduce the likelihood of progression. For some women, in-patient management will however be unavoidable as critical OHSS and severe OHSS with persistent haemoconcentration and dehydration will require multidisciplinary care and potentially intensive care.

## **Conclusions**

Successful mitigation of the risk of OHSS is now feasible. Biomarkers have enabled pre-treatment stratification of risk, with the use of GnRH antagonist protocols with a GnRH agonist trigger and elective cryopreservation of all embryos a particularly effective strategy. Other strategies including cabergoline and calcium gluconate are useful if proceeding to a fresh embryo transfer. In the absence of effective OHSS preventative strategies, fluid resuscitation, supportive care, paracentesis and prophylactic anticoagulation are recommended.

**Conflict of Interest**

The authour has received speaker fees and participated in Advisory Boards for Beckman Coulter, Ferring, Merck KGaA, Merck & Co, Roche Diagnostics and Finox.



**Figure 1:** Ovarian hyperstimulation syndrome (OHSS) flow diagram for use in the clinical trial setting. †Exaggerated response, as defined by World Health Organization criteria. ‡Subjects to be screened for OHSS symptoms on the day of embryo transfer, the day of positive pregnancy test or at the time of complaint. Shaded shapes denote required reporting of group in the context of a clinical trial. LFT, liver function test; AST, aspartate aminotransferase; ALT, alanine aminotransferase; GGT, gamma-glutamyl transferase; Cr, creatinine. Adapted from [4]

Category	Features
<b>Mild OHSS</b>	Abdominal bloating
	Mild abdominal pain
	Ovarian size usually < 8 cm <sup>†</sup>
<b>Moderate OHSS</b>	Moderate abdominal pain
	Nausea ± vomiting
	Ultrasound evidence of ascites
	Ovarian size usually 8–12 cm <sup>†</sup>
<b>Severe OHSS</b>	Clinical ascites (± hydrothorax)
	Oliguria (< 300 ml/day or < 30 ml/hour)
	Haematocrit > 0.45
	Hyponatraemia (sodium < 135 mmol/l)
	Hypo-osmolality (osmolality < 282 mOsm/kg)
	Hyperkalaemia (potassium > 5 mmol/l)
	Hypoproteinaemia (serum albumin < 35 g/l)
	Ovarian size usually > 12 cm <sup>†</sup>
<b>Critical OHSS</b>	
	Tense ascites/large hydrothorax
	Haematocrit > 0.55
	White cell count > 25,000/ml
	Oliguria/anuria
	Thromboembolism
	Acute respiratory distress syndrome

<sup>†</sup> Ovarian size may not correlate with severity of OHSS in cases of assisted reproduction because of the effect of follicular aspiration. Women demonstrating any feature of severe or critical OHSS should be classified in that category.

**Table 1:** RCOG classification of severity of OHSS.

Adapted from [3]

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